(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 November 2002 (28.11.2002)

PCT

(10) International Publication Number
WO 02/095704 A1

(51) International Patent Classification[7]: G08B 21/00

(21) International Application Number: PCT/US02/15859

(22) International Filing Date: 17 May 2002 (17.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/292,495 21 May 2001 (21.05.2001) US

(71) Applicant *(for all designated States except US)*: **ALCON, INC.** [CH/CH]; Bosch 69, P. O. Box 62, CH-6331 Hunenberg (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GAMACHE, Daniel, A.** [US/US]; 5610 Hunterwood Lane, Arlington, TX 76017 (US). **YANNI, John, M.** [US/US]; 2821 Donnybrook Drive, Burleson, TX 76028 (US).

(74) Agents: **RYAN, Patrick, M.** et al.; Alcon Research, Ltd., R & D Counsel Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).

(81) Designated States *(national)*: AU, BR, CA, CN, JP, MX, PL, US, ZA.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/095704 A1

(54) Title: USE OF NFKB INHIBITORS TO TREAT DRY EYE DISORDERS

(57) Abstract: NF-kB inhibitors are useful for treating dry eye disorders and other disorders requiring the wetting of the eye.

Use of NF-κB Inhibitors to Treat Dry Eye Disorders

The present invention is directed to the treatment of dry eye disorders. In particular, the present invention is directed to the use of NF-κB inhibitors in the treatment of dry eye and other disorders requiring the wetting of the eye in mammals.

Background of the Invention

Dry eye, also known generically as *keratoconjunctivitis sicca,* is a common ophthalmological disorder affecting millions of Americans each year. The condition is particularly widespread among post-menopausal women due to hormonal changes following the cessation of fertility. Dry eye may afflict an individual with varying severity. In mild cases, a patient may experience burning, a feeling of dryness, and persistent irritation such as is often caused by small bodies lodging between the eye lid and the eye surface. In severe cases, vision may be substantially impaired. Other diseases, such as Sjogren's disease and *cicatricial pemphigoid* manifest dry eye complications.

Although it appears that dry eye may result from a number of unrelated pathogenic causes, all presentations of the complication share a common effect, that is the breakdown of the pre-ocular tear film, which results in dehydration of the exposed outer surface and many of the symptoms outlined above (Lemp, *Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes,* The CLAO Journal, volume 21, number 4, pages 221-231 (1995)).

Practitioners have taken several approaches to the treatment of dry eye. One common approach has been to supplement and stabilize the ocular

tear film using so-called artificial tears instilled throughout the day. Other approaches include the use of ocular inserts that provide a tear substitute or stimulation of endogenous tear production.

Examples of the tear substitution approach include the use of buffered, isotonic saline solutions, aqueous solutions containing water soluble polymers that render the solutions more viscous and thus less easily shed by the eye. Tear reconstitution is also attempted by providing one or more components of the tear film such as phospholipids and oils. Phospholipid compositions have been shown to be useful in treating dry eye; see, e.g., McCulley and Shine, *Tear film structure and dry eye*, Contactologia, volume 20(4), pages 145-49 (1998); and Shine and McCulley, *Keratoconjunctivitis sicca associated with meibomian secretion polar lipid abnormality*, Archives of Ophthalmology, volume 116(7), pages 849-52 (1998). Examples of phospholipid compositions for the treatment of dry eye are disclosed in U.S. Patent Nos. 4,131,651 (Shah et al.), 4,370,325 (Packman), 4,409,205 (Shively), 4,744,980 and 4,883,658 (Holly), 4,914,088 (Glonek), 5,075,104 (Gressel et al.), 5,278,151 (Korb et al.), 5,294,607 (Glonek et al.), 5,371,108 (Korb et al.) and 5,578,586 (Glonek et al.). U.S. Patent No. 5,174,988 (Mautone et al.) discloses phospholipid drug delivery systems involving phospholipids, propellants and an active substance.

Another approach involves the provision of lubricating substances in lieu of artificial tears. For example, U.S. Patent No. 4,818,537 (Guo) discloses the use of a lubricating, liposome-based composition, and U.S. Patent No. 5,800,807 (Hu et al.) discloses compositions containing glycerin and propylene glycol for treating dry eye.

Although these approaches have met with some success, problems in the treatment of dry eye nevertheless remain. The use of tear substitutes,

while temporarily effective, generally requires repeated application over the course of a patient's waking hours. It is not uncommon for a patient to have to apply artificial tear solution ten to twenty times over the course of the day. Such an undertaking is not only cumbersome and time consuming, but is also potentially very expensive. Transient symptoms of dry eye associated with refractive surgery have been reported to last in some cases from six weeks to six months or more following surgery.

Aside from efforts directed primarily to the alleviation of symptoms associated with dry eye, methods and compositions directed to treatment of the dry eye condition have also been pursued. For example, U.S. Patent No. 5,041,434 (Lubkin) discloses the use of sex steroids, such as conjugated estrogens, to treat dry eye conditions in post-menopausal women; U.S. Patent No. 5,290,572 (MacKeen) discloses the use of finely divided calcium ion compositions to stimulate pre-ocular tear film production; and U.S. Patent No. 4,966,773 (Gressel et al.) discloses the use of microfine particles of one or more retinoids for ocular tissue normalization.

Some recent literature reports suggest that patients suffering from dry eye syndrome disproportionately exhibit the hallmarks of excessive inflammation in relevant ocular tissues, such as the lacrimal and meibomian glands. The use of various compounds to treat dry eye patients, such as steroids [*e.g.* U.S. Patent No. 5,958,912; Marsh, et al., *Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjogren syndrome*, Ophthalmology, 106(4): 811-816 (1999); Pflugfelder, *et. al.* U.S. Patent No. 6,153,607], cytokine release inhibitors (Yanni, J.M.; *et. al.* WO 0003705 A1), cyclosporine A [Tauber, J. *Adv. Exp. Med. Biol.* **1998**, *438* (Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2), 969], and 15-HETE (Yanni *et. al.*, US Patent No. 5,696,166), has been disclosed.

Inflammatory processes are known to involve the upregulation of several gene products by the nuclear transcription factor, NF-κB. In its quiescent state NF-κB exists as a heterodimer with the protein Iκ-Bα, which masks the nuclear localization signals and DNA binding domain of the former protein. Under inflammatory conditions Iκ-Bα is phosphorylated, causing a conformational change which results in its tagging with multiple copies of the ubiquitin protein. Ubiquinated Iκ-Bα is recognized and degraded by the proteasome, which liberates NF-κB. The free protein is translocated to the nucleus, where it binds to the appropriate DNA sequence and upregulates the production of several inflammatory mediators, such as COX-2, iNOS, IL-1, and TNF-α. Therefore, inhibitors of the synthesis, activation, translocation or DNA binding activity of NF-κB could reduce inflammation and provide therapeutic benefit to dry eye patients.

Summary of the Invention

The present invention is directed to methods for the treatment of dry eye and other disorders requiring the wetting of the eye, including symptoms of dry eye associated with refractive surgery such as LASIK surgery. According to the methods of the present invention, NF-κB inhibitors are administered to a patient suffering from dry eye or other disorders requiring wetting of the eye. The NF-κB inhibitors are preferably administered topically to the eye.

Detailed Description of the Invention

As used herein, "NF-κB inhibitors" means compounds that prevent the synthesis, activation, translocation and/or DNA binding activity of NF-κB. Although some steroids act as NF-κB inhibitors, for purposes of the present invention "NF-κB inhibitor" does not include any steroids.

NF-κB inhibitors are known. Examples of NF-κB inhibitors useful in the methods of the present invention include 2-chloro-N-[3,5-di(trifluoromethyl)phenyl]-4-(trifluoromethyl)pyrimidine-5-carboxamide (also known as SP-100030); 3,4-dihydro-4,4-dimethyl-2H-1,2-benzoselenazine (also known as BXT-51072); declopramide (also known as Oxi-104); and dexlipotam.

According to the methods of the present invention, a composition comprising one or more NF-κB inhibitors and a pharmaceutically acceptable carrier for topical ophthalmic administration or implantation into the conjunctival sac or anterior chamber of the eye is administered to a mammal in need thereof. The compositions are formulated in accordance with methods known in the art for the particular route of administration desired.

The compositions administered according to the present invention comprise a pharmaceutically effective amount of one or more NF-κB inhibitors. As used herein, a "pharmaceutically effective amount" is one which is sufficient to reduce or eliminate signs or symptoms of dry eye or other disorders requiring the wetting of the eye. Generally, for compositions intended to be administered topically to the eye in the form of eye drops or eye ointments, the total amount of NF-κB inhibitor will be about 0.001 to 1.0% (w/v).

Preferably, the compositions administered according to the present invention will be formulated as solutions, suspensions and other dosage forms for topical administration. Aqueous solutions are generally preferred, based on ease of formulation, as well as a patient's ability to easily administer such compositions by means of instilling one to two drops of the solutions in the affected eyes. However, the compositions may also be suspensions,

viscous or semi-viscous gels, or other types of solid or semi-solid compositions. Suspensions may be preferred for NF-κB inhibitors which are sparingly soluble in water.

The compositions administered according to the present invention may also include various other ingredients, including but not limited to surfactants, tonicity agents, buffers, preservatives, co-solvents and viscosity building agents.

Various tonicity agents may be employed to adjust the tonicity of the composition, preferably to that of natural tears for ophthalmic compositions. For example, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, dextrose and/or mannitol may be added to the composition to approximate physiological tonicity. Such an amount of tonicity agent will vary, depending on the particular agent to be added. In general, however, the compositions will have a tonicity agent in an amount sufficient to cause the final composition to have an ophthalmically acceptable osmolality (generally about 150 – 450 mOsm, preferably 250 – 350 mOsm).

An appropriate buffer system (e.g., sodium phosphate, sodium acetate, sodium citrate, sodium borate or boric acid) may be added to the compositions to prevent pH drift under storage conditions. The particular concentration will vary, depending on the agent employed. Preferably, however, the buffer will be chosen to maintain a target pH within the range of pH 6-7.5.

Compositions formulated for the treatment of dry eye-type diseases and disorders may also comprise aqueous carriers designed to provide immediate, short-term relief of dry eye-type conditions. Such carriers can be formulated as a phospholipid carrier or an artificial tears carrier, or mixtures of both. As used herein, "phospholipid carrier" and "artificial tears carrier" refer

to aqueous compositions which: (i) comprise one or more phospholipids (in the case of phospholipid carriers) or other compounds, which lubricate, "wet," approximate the consistency of endogenous tears, aid in natural tear build-up, or otherwise provide temporary relief of dry eye symptoms and conditions upon ocular administration; (ii) are safe; and (iii) provide the appropriate delivery vehicle for the topical administration of an effective amount of one or more NF-κB inhibitors. Examples or artificial tears compositions useful as artificial tears carriers include, but are not limited to, commercial products, such as Tears Naturale®, Tears Naturale II®, Tears Naturale Free®, and Bion Tears® (Alcon Laboratories, Inc., Fort Worth, Texas). Examples of phospholipid carrier formulations include those disclosed in U.S. Patent Nos. 4,804,539 (Guo et al.), 4,883,658 (Holly), 4,914,088 (Glonek), 5,075,104 (Gressel et al.), 5,278,151 (Korb et al.), 5,294,607 (Glonek et al.), 5,371,108 (Korb et al.), 5,578,586 (Glonek et al.); the foregoing patents are incorporated herein by reference to the extent they disclose phospholipid compositions useful as phospholipid carriers of the present invention.

Other compounds designed to lubricate, "wet," approximate the consistency of endogenous tears, aid in natural tear build-up, or otherwise provide temporary relief of dry eye symptoms and conditions upon ocular administration the eye are known in the art. Such compounds may enhance the viscosity of the composition, and include, but are not limited to: monomeric polyols, such as, glycerol, propylene glycol, ethylene glycol; polymeric polyols, such as, polyethylene glycol, hydroxypropylmethyl cellulose ("HPMC"), carboxy methylcellulose sodium, hydroxy propylcellulose ("HPC"), dextrans, such as, dextran 70; water soluble proteins, such as gelatin; and vinyl polymers, such as, polyvinyl alcohol, polyvinylpyrrolidone, povidone and carbomers, such as, carbomer 934P, carbomer 941, carbomer 940, carbomer 974P.

Other compounds may also be added to the ophthalmic compositions of the present invention to increase the viscosity of the carrier. Examples of viscosity enhancing agents include, but are not limited to: polysaccharides, such as hyaluronic acid and its salts, chondroitin sulfate and its salts, dextrans, various polymers of the cellulose family; vinyl polymers; and acrylic acid polymers. In general, the phospholipid carrier or artificial tears carrier compositions will exhibit a viscosity of 1 to 400 centipoises ("cps").

Topical ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, chlorobutanol, benzododecinium bromide, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, polyquaternium-1, or other agents known to those skilled in the art. Such preservatives are typically employed at a level of from 0.001 to 1.0% w/v. Unit dose compositions of the present invention will be sterile, but typically unpreserved. Such compositions, therefore, generally will not contain preservatives.

The preferred compositions of the present invention are intended for administration to a human patient suffering from dry eye or symptoms of dry eye. Preferably, such compositions will be administered topically. In general, the doses used for the above described purposes will vary, but will be in an effective amount to eliminate or improve dry eye conditions. Generally, 1-2 drops of such compositions will be administered from once to many times per day.

A representative eye drop formulation is provided in Example 1 below.

Example 1

Ingredient	Amount (% w/v)
NF-κB inhibitor	0.001-1.0
Polyoxyl 40 Stearate	0.1
Boric Acid	0.25
Sodium Chloride	0.75
Disodium Edetate	0.01
Polyquaternium-1	0.001
NaOH/HCl	q.s., pH = 7.4
Purified Water	q.s. 100%

The above composition is prepared by the following method. The batch quantities of boric acid, sodium chloride, disodium edetate, and polyquaternium-1 are weighed and dissolved by stirring in 90% of the batch quantity of purified water. The pH is adjusted to 7.4 ± 0.1 with NaOH and/or HCl. The batch quantity of the NF-κB inhibitor as a stock solution is measured and added. Purified water is added to q.s. to 100%. The mixture is stirred for five minutes to homogenize and then filtered through a sterilizing filter membrane into a sterile recipient.

This invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its special or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

WHAT IS CLAIMED IS:

1. A method for the treatment of dry eye and other disorders requiring the wetting of the eye which comprises administering to a mammal a composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of one or more NF-κB inhibitors.

2. The method of Claim 1 wherein the pharmaceutically effective amount of one or more NF-κB inhibitors is 0.001 – 1.0% (w/v).

3. The method of Claim 1 wherein the NF-κB inhibitor is selected from the group consisting of: 2-chloro-N-[3,5-di(trifluoromethyl)phenyl]-4-(trifluoromethyl)pyrimidine-5-carboxamide; 3,4-dihydro-4,4-dimethyl-2H-1,2-benzoselenazine; declopramide; and dexlipotam.

4. The method of Claim 1 wherein the composition is topically administered to the eye.

5. The method of Claim 1 wherein the dry eye and other disorders requiring the wetting of the eye is symptoms of dry eye associated with refractive surgery.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/15859

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G08B21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G08B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 043 747 A (ALTENHOFEN CYNTHIA L) 28 March 2000 (2000-03-28) column 4, line 18 -column 6, line 62; figures 1-5	1-48
A	US 5 280 635 A (KNOEDLER ROY E ET AL) 18 January 1994 (1994-01-18) abstract	16-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 September 2002	20/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sgura, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/15859

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6043747 A	28-03-2000	NONE	
US 5280635 A	18-01-1994	AU 2553792 A	05-04-1993
		WO 9305581 A1	18-03-1993

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 November 2002 (28.11.2002)

PCT

(10) International Publication Number
WO 02/095704 A1

(51) International Patent Classification[7]: A61K 31/165, 31/505, A61P 27/02, A61K 31/395

(21) International Application Number: PCT/US02/15859

(22) International Filing Date: 17 May 2002 (17.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/292,495 21 May 2001 (21.05.2001) US

(71) Applicant *(for all designated States except US)*: ALCON, INC. [CH/CH]; Bosch 69, P. O. Box 62, CH-6331 Hunenberg (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: GAMACHE, Daniel, A. [US/US]; 5610 Hunterwood Lane, Arlington, TX 76017 (US). YANNI, John, M. [US/US]; 2821 Donnybrook Drive, Burleson, TX 76028 (US).

(74) Agents: RYAN, Patrick, M. et al.; Alcon Research, Ltd., R & D Counsel Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).

(81) Designated States *(national)*: AU, BR, CA, CN, JP, MX, PL, US, ZA.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
— *with international search report*

(48) Date of publication of this corrected version:
27 February 2003

(15) Information about Correction:
see PCT Gazette No. 09/2003 of 27 February 2003, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/095704 A1

(54) Title: USE OF NF-KAPPA-B INHIBITORS TO TREAT DRY EYE DISORDERS

(57) Abstract: NF-kB inhibitors are useful for treating dry eye disorders and other disorders requiring the wetting of the eye.

Use of NF-κB Inhibitors to Treat Dry Eye Disorders

The present invention is directed to the treatment of dry eye disorders. In particular, the present invention is directed to the use of NF-κB inhibitors in the treatment of dry eye and other disorders requiring the wetting of the eye in mammals.

Background of the Invention

Dry eye, also known generically as *keratoconjunctivitis sicca,* is a common ophthalmological disorder affecting millions of Americans each year. The condition is particularly widespread among post-menopausal women due to hormonal changes following the cessation of fertility. Dry eye may afflict an individual with varying severity. In mild cases, a patient may experience burning, a feeling of dryness, and persistent irritation such as is often caused by small bodies lodging between the eye lid and the eye surface. In severe cases, vision may be substantially impaired. Other diseases, such as Sjogren's disease and *cicatricial pemphigoid* manifest dry eye complications.

Although it appears that dry eye may result from a number of unrelated pathogenic causes, all presentations of the complication share a common effect, that is the breakdown of the pre-ocular tear film, which results in dehydration of the exposed outer surface and many of the symptoms outlined above (Lemp, *Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes*, The CLAO Journal, volume 21, number 4, pages 221-231 (1995)).

Practitioners have taken several approaches to the treatment of dry eye. One common approach has been to supplement and stabilize the ocular

tear film using so-called artificial tears instilled throughout the day. Other approaches include the use of ocular inserts that provide a tear substitute or stimulation of endogenous tear production.

Examples of the tear substitution approach include the use of buffered, isotonic saline solutions, aqueous solutions containing water soluble polymers that render the solutions more viscous and thus less easily shed by the eye. Tear reconstitution is also attempted by providing one or more components of the tear film such as phospholipids and oils. Phospholipid compositions have been shown to be useful in treating dry eye; see, e.g., McCulley and Shine, *Tear film structure and dry eye*, Contactologia, volume 20(4), pages 145-49 (1998); and Shine and McCulley, *Keratoconjunctivitis sicca associated with meibomian secretion polar lipid abnormality*, Archives of Ophthalmology, volume 116(7), pages 849-52 (1998). Examples of phospholipid compositions for the treatment of dry eye are disclosed in U.S. Patent Nos. 4,131,651 (Shah et al.), 4,370,325 (Packman), 4,409,205 (Shively), 4,744,980 and 4,883,658 (Holly), 4,914,088 (Glonek), 5,075,104 (Gressel et al.), 5,278,151 (Korb et al.), 5,294,607 (Glonek et al.), 5,371,108 (Korb et al.) and 5,578,586 (Glonek et al.). U.S. Patent No. 5,174,988 (Mautone et al.) discloses phospholipid drug delivery systems involving phospholipids, propellants and an active substance.

Another approach involves the provision of lubricating substances in lieu of artificial tears. For example, U.S. Patent No. 4,818,537 (Guo) discloses the use of a lubricating, liposome-based composition, and U.S. Patent No. 5,800,807 (Hu et al.) discloses compositions containing glycerin and propylene glycol for treating dry eye.

Although these approaches have met with some success, problems in the treatment of dry eye nevertheless remain. The use of tear substitutes,

while temporarily effective, generally requires repeated application over the course of a patient's waking hours. It is not uncommon for a patient to have to apply artificial tear solution ten to twenty times over the course of the day. Such an undertaking is not only cumbersome and time consuming, but is also potentially very expensive. Transient symptoms of dry eye associated with refractive surgery have been reported to last in some cases from six weeks to six months or more following surgery.

Aside from efforts directed primarily to the alleviation of symptoms associated with dry eye, methods and compositions directed to treatment of the dry eye condition have also been pursued. For example, U.S. Patent No. 5,041,434 (Lubkin) discloses the use of sex steroids, such as conjugated estrogens, to treat dry eye conditions in post-menopausal women; U.S. Patent No. 5,290,572 (MacKeen) discloses the use of finely divided calcium ion compositions to stimulate pre-ocular tear film production; and U.S. Patent No. 4,966,773 (Gressel et al.) discloses the use of microfine particles of one or more retinoids for ocular tissue normalization.

Some recent literature reports suggest that patients suffering from dry eye syndrome disproportionately exhibit the hallmarks of excessive inflammation in relevant ocular tissues, such as the lacrimal and meibomian glands. The use of various compounds to treat dry eye patients, such as steroids [*e.g.* U.S. Patent No. 5,958,912; Marsh, et al., *Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjogren syndrome*, Ophthalmology, 106(4): 811-816 (1999); Pflugfelder, *et. al.* U.S. Patent No. 6,153,607], cytokine release inhibitors (Yanni, J.M.; *et. al.* WO 0003705 A1), cyclosporine A [Tauber, J. *Adv. Exp. Med. Biol.* **1998**, *438* (Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2), 969], and 15-HETE (Yanni *et. al.*, US Patent No. 5,696,166), has been disclosed.

Inflammatory processes are known to involve the upregulation of several gene products by the nuclear transcription factor, NF-κB. In its quiescent state NF-κB exists as a heterodimer with the protein Iκ-Bα, which masks the nuclear localization signals and DNA binding domain of the former protein. Under inflammatory conditions Iκ-Bα is phosphorylated, causing a conformational change which results in its tagging with multiple copies of the ubiquitin protein. Ubiquinated Iκ-Bα is recognized and degraded by the proteasome, which liberates NF-κB. The free protein is translocated to the nucleus, where it binds to the appropriate DNA sequence and upregulates the production of several inflammatory mediators, such as COX-2, iNOS, IL-1, and TNF-α. Therefore, inhibitors of the synthesis, activation, translocation or DNA binding activity of NF-κB could reduce inflammation and provide therapeutic benefit to dry eye patients.

Summary of the Invention

The present invention is directed to methods for the treatment of dry eye and other disorders requiring the wetting of the eye, including symptoms of dry eye associated with refractive surgery such as LASIK surgery. According to the methods of the present invention, NF-κB inhibitors are administered to a patient suffering from dry eye or other disorders requiring wetting of the eye. The NF-κB inhibitors are preferably administered topically to the eye.

Detailed Description of the Invention

As used herein, "NF-κB inhibitors" means compounds that prevent the synthesis, activation, translocation and/or DNA binding activity of NF-κB. Although some steroids act as NF-κB inhibitors, for purposes of the present invention "NF-κB inhibitor" does not include any steroids.

NF-κB inhibitors are known. Examples of NF-κB inhibitors useful in the methods of the present invention include 2-chloro-N-[3,5-di(trifluoromethyl)phenyl]-4-(trifluoromethyl)pyrimidine-5-carboxamide (also known as SP-100030); 3,4-dihydro-4,4-dimethyl-2H-1,2-benzoselenazine (also known as BXT-51072); declopramide (also known as Oxi-104); and dexlipotam.

According to the methods of the present invention, a composition comprising one or more NF-κB inhibitors and a pharmaceutically acceptable carrier for topical ophthalmic administration or implantation into the conjunctival sac or anterior chamber of the eye is administered to a mammal in need thereof. The compositions are formulated in accordance with methods known in the art for the particular route of administration desired.

The compositions administered according to the present invention comprise a pharmaceutically effective amount of one or more NF-κB inhibitors. As used herein, a "pharmaceutically effective amount" is one which is sufficient to reduce or eliminate signs or symptoms of dry eye or other disorders requiring the wetting of the eye. Generally, for compositions intended to be administered topically to the eye in the form of eye drops or eye ointments, the total amount of NF-κB inhibitor will be about 0.001 to 1.0% (w/v).

Preferably, the compositions administered according to the present invention will be formulated as solutions, suspensions and other dosage forms for topical administration. Aqueous solutions are generally preferred, based on ease of formulation, as well as a patient's ability to easily administer such compositions by means of instilling one to two drops of the solutions in the affected eyes. However, the compositions may also be suspensions,

viscous or semi-viscous gels, or other types of solid or semi-solid compositions. Suspensions may be preferred for NF-κB inhibitors which are sparingly soluble in water.

The compositions administered according to the present invention may also include various other ingredients, including but not limited to surfactants, tonicity agents, buffers, preservatives, co-solvents and viscosity building agents.

Various tonicity agents may be employed to adjust the tonicity of the composition, preferably to that of natural tears for ophthalmic compositions. For example, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, dextrose and/or mannitol may be added to the composition to approximate physiological tonicity. Such an amount of tonicity agent will vary, depending on the particular agent to be added. In general, however, the compositions will have a tonicity agent in an amount sufficient to cause the final composition to have an ophthalmically acceptable osmolality (generally about 150 – 450 mOsm, preferably 250 – 350 mOsm).

An appropriate buffer system (e.g., sodium phosphate, sodium acetate, sodium citrate, sodium borate or boric acid) may be added to the compositions to prevent pH drift under storage conditions. The particular concentration will vary, depending on the agent employed. Preferably, however, the buffer will be chosen to maintain a target pH within the range of pH 6-7.5.

Compositions formulated for the treatment of dry eye-type diseases and disorders may also comprise aqueous carriers designed to provide immediate, short-term relief of dry eye-type conditions. Such carriers can be formulated as a phospholipid carrier or an artificial tears carrier, or mixtures of both. As used herein, "phospholipid carrier" and "artificial tears carrier" refer

to aqueous compositions which: (i) comprise one or more phospholipids (in the case of phospholipid carriers) or other compounds, which lubricate, "wet," approximate the consistency of endogenous tears, aid in natural tear build-up, or otherwise provide temporary relief of dry eye symptoms and conditions upon ocular administration; (ii) are safe; and (iii) provide the appropriate delivery vehicle for the topical administration of an effective amount of one or more NF-κB inhibitors. Examples or artificial tears compositions useful as artificial tears carriers include, but are not limited to, commercial products, such as Tears Naturale®, Tears Naturale II®, Tears Naturale Free®, and Bion Tears® (Alcon Laboratories, Inc., Fort Worth, Texas). Examples of phospholipid carrier formulations include those disclosed in U.S. Patent Nos. 4,804,539 (Guo et al.), 4,883,658 (Holly), 4,914,088 (Glonek), 5,075,104 (Gressel et al.), 5,278,151 (Korb et al.), 5,294,607 (Glonek et al.), 5,371,108 (Korb et al.), 5,578,586 (Glonek et al.); the foregoing patents are incorporated herein by reference to the extent they disclose phospholipid compositions useful as phospholipid carriers of the present invention.

Other compounds designed to lubricate, "wet," approximate the consistency of endogenous tears, aid in natural tear build-up, or otherwise provide temporary relief of dry eye symptoms and conditions upon ocular administration the eye are known in the art. Such compounds may enhance the viscosity of the composition, and include, but are not limited to: monomeric polyols, such as, glycerol, propylene glycol, ethylene glycol; polymeric polyols, such as, polyethylene glycol, hydroxypropylmethyl cellulose ("HPMC"), carboxy methylcellulose sodium, hydroxy propylcellulose ("HPC"), dextrans, such as, dextran 70; water soluble proteins, such as gelatin; and vinyl polymers, such as, polyvinyl alcohol, polyvinylpyrrolidone, povidone and carbomers, such as, carbomer 934P, carbomer 941, carbomer 940, carbomer 974P.

Other compounds may also be added to the ophthalmic compositions of the present invention to increase the viscosity of the carrier. Examples of viscosity enhancing agents include, but are not limited to: polysaccharides, such as hyaluronic acid and its salts, chondroitin sulfate and its salts, dextrans, various polymers of the cellulose family; vinyl polymers; and acrylic acid polymers. In general, the phospholipid carrier or artificial tears carrier compositions will exhibit a viscosity of 1 to 400 centipoises ("cps").

Topical ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, chlorobutanol, benzododecinium bromide, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, polyquaternium-1, or other agents known to those skilled in the art. Such preservatives are typically employed at a level of from 0.001 to 1.0% w/v. Unit dose compositions of the present invention will be sterile, but typically unpreserved. Such compositions, therefore, generally will not contain preservatives.

The preferred compositions of the present invention are intended for administration to a human patient suffering from dry eye or symptoms of dry eye. Preferably, such compositions will be administered topically. In general, the doses used for the above described purposes will vary, but will be in an effective amount to eliminate or improve dry eye conditions. Generally, 1-2 drops of such compositions will be administered from once to many times per day.

A representative eye drop formulation is provided in Example 1 below.

Example 1

Ingredient	Amount (% w/v)
NF-κB inhibitor	0.001-1.0
Polyoxyl 40 Stearate	0.1
Boric Acid	0.25
Sodium Chloride	0.75
Disodium Edetate	0.01
Polyquaternium-1	0.001
NaOH/HCl	q.s., pH = 7.4
Purified Water	q.s. 100%

The above composition is prepared by the following method. The batch quantities of boric acid, sodium chloride, disodium edetate, and polyquaternium-1 are weighed and dissolved by stirring in 90% of the batch quantity of purified water. The pH is adjusted to 7.4 ± 0.1 with NaOH and/or HCl. The batch quantity of the NF-κB inhibitor as a stock solution is measured and added. Purified water is added to q.s. to 100%. The mixture is stirred for five minutes to homogenize and then filtered through a sterilizing filter membrane into a sterile recipient.

This invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its special or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

WHAT IS CLAIMED IS:

1. A method for the treatment of dry eye and other disorders requiring the wetting of the eye which comprises administering to a mammal a composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of one or more NF-κB inhibitors.

2. The method of Claim 1 wherein the pharmaceutically effective amount of one or more NF-κB inhibitors is 0.001 – 1.0% (w/v).

3. The method of Claim 1 wherein the NF-κB inhibitor is selected from the group consisting of: 2-chloro-N-[3,5-di(trifluoromethyl)phenyl]-4-(trifluoromethyl)pyrimidine-5-carboxamide; 3,4-dihydro-4,4-dimethyl-2H-1,2-benzoselenazine; declopramide; and dexlipotam.

4. The method of Claim 1 wherein the composition is topically administered to the eye.

5. The method of Claim 1 wherein the dry eye and other disorders requiring the wetting of the eye is symptoms of dry eye associated with refractive surgery.

XCID: <WO 02095704A1 IA>

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/~~17301~~ 15859

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/165 A61K31/505 A61P27/02 A61K31/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EPO-Internal, CHEM ABS Data, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FRIEDLAENDER M H: "OCULAR MANIFESTATIONS OF SJOGREN'S SYNDROME KERATOCONJUNCTIVITIS SICCA" RHEUMATIC DISEASE CLINICS OF NORTH AMERICA, vol. 18, no. 3, 1992, pages 591-608, XP002214413 ISSN: 0889-857X page 591, line 19 --- -/--	1-5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 October 2002	29/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allnutt, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/[redacted] 15859

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	LANGE R W: "BXT-51072 OXIS International" CURRENT OPINION IN ANTIINFLAMMATORY AND IMMUNOMODULATORY INVESTIGATIONAL DRUGS, vol. 2, no. 4, 2000, pages 338-341, XP001105133 page 338, column 1, line 24,49 page 338, column 2, line 15-1 page 340, column 1, line 5 page 340, column 2, line 2	1-5
Y	US 5 968 920 A (YADAN JEAN-CLAUDE ET AL) 19 October 1999 (1999-10-19) page 8, line 27; claims 5,9; example 8	1-5
A	LIBERG D ET AL: "N-substituted benzamides inhibit NFkappaB activation and induce apoptosis by separate mechanisms." BRITISH JOURNAL OF CANCER, vol. 81, no. 6, November 1999 (1999-11), pages 981-988, XP001037954 ISSN: 0007-0920 Last line of abstract page 987, column 1, line 16-19	1-5
A	GOLDMAN M E; RANSONE L J; ANDERSON D W; ET AL: "SP100030 is a novel Tcell specific transcription factor inhibitor that possesses immunosuppressive activity in vivo." TRANSPLANTATION PROCEEDINGS, vol. 28, no. 6, December 1996 (1996-12), pages 3106-3109, XP002215678 See whole document	1-5

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/US 02/[redacted] 15859

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-5 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Continuation of Box I.2

Claims Nos.: 1

Present claim 1 relates to compounds defined by reference to a desirable characteristic or property, namely 'NFkappa-B inhibitors'.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.
Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds defined in claim 3:
2-chloro-N-'3,5-di(trifluoromethyl)phenyl!-4-(trifluoromethyl)pyrimidine-5-carboxamide; 3,4-dihydro-4,4-dimethyl-2H-1,2-benzoselenazine; declopramide; and dexlipotam in addition to known defined NF-kappa-B inhibitors.
The applicants attention is drawn to the fact that some compounds may be already known to treat the diseases/disorders claimed by the applicant but are as yet not identified as NF-kappa-B inhibitors.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/[redacted] 10859

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5968920 A	19-10-1999	FR	2718441 A1	13-10-1995
		AU	692542 B2	11-06-1998
		AU	2311195 A	30-10-1995
		CA	2164642 A1	19-10-1995
		DE	69521465 D1	02-08-2001
		DE	69521465 T2	29-05-2002
		DE	701554 T1	10-10-1996
		DK	701554 T3	08-10-2001
		EP	0701554 A1	20-03-1996
		ES	2161879 T3	16-12-2001
		WO	9527706 A1	19-10-1995
		JP	11501005 T	26-01-1999
		US	6093532 A	25-07-2000

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

REVISED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 November 2002 (28.11.2002)

PCT

(10) International Publication Number
WO 02/095704 A1

(51) International Patent Classification[7]: A61K 31/165, 31/505, A61P 27/02, A61K 31/395

(21) International Application Number: PCT/US02/15859

(22) International Filing Date: 17 May 2002 (17.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/292,495 21 May 2001 (21.05.2001) US

(71) Applicant *(for all designated States except US)*: **ALCON, INC.** [CH/CH]; Bosch 69, P. O. Box 62, CH-6331 Hunenberg (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **GAMACHE, Daniel, A.** [US/US]; 5610 Hunterwood Lane, Arlington, TX 76017 (US). **YANNI, John, M.** [US/US]; 2821 Donnybrook Drive, Burleson, TX 76028 (US).

(74) Agents: **RYAN, Patrick, M.** et al.; Alcon Research, Ltd., R & D Counsel Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).

(81) Designated States *(national)*: AU, BR, CA, CN, JP, MX, PL, US, ZA.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
— *with international search report*

(88) Date of publication of the revised international search report: 18 September 2003

(15) Information about Corrections:
see PCT Gazette No. 38/2003 of 18 September 2003, Section II
Previous Correction:
see PCT Gazette No. 09/2003 of 27 February 2003, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/095704 A1

(54) Title: USE OF NF-KAPPA-B INHIBITORS TO TREAT DRY EYE DISORDERS

(57) Abstract: NF-kB inhibitors are useful for treating dry eye disorders and other disorders requiring the wetting of the eye.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 02/15859

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/165 A61K31/505 A61P27/02 A61K31/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FRIEDLAENDER M H: "OCULAR MANIFESTATIONS OF SJOGREN'S SYNDROME KERATOCONJUNCTIVITIS SICCA" RHEUMATIC DISEASE CLINICS OF NORTH AMERICA, vol. 18, no. 3, 1992, pages 591-608, XP002214413 ISSN: 0889-857X page 591, line 19 --- -/--	1-5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 October 2002	29. 07. 03

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allnutt, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/15859

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LANGE R W: "BXT-51072 OXIS International" CURRENT OPINION IN ANTIINFLAMMATORY AND IMMUNOMODULATORY INVESTIGATIONAL DRUGS, vol. 2, no. 4, 2000, pages 338-341, XP001105133 page 338, column 1, line 24,49 page 338, column 2, line 15-1 page 340, column 1, line 5 page 340, column 2, line 2 ---	1-5
Y	US 5 968 920 A (YADAN JEAN-CLAUDE ET AL) 19 October 1999 (1999-10-19) page 8, line 27; claims 5,9; example 8 ---	1-5
A	LIBERG D ET AL: "N-substituted benzamides inhibit NFkappaB activation and induce apoptosis by separate mechanisms." BRITISH JOURNAL OF CANCER, vol. 81, no. 6, November 1999 (1999-11), pages 981-988, XP001037954 ISSN: 0007-0920 Last line of abstract page 987, column 1, line 16-19 ---	1-5
A	GOLDMAN M E; RANSONE L J; ANDERSON D W; ET AL: "SP100030 is a novel Tcell specific transcription factor inhibitor that possesses immunosuppressive activity in vivo." TRANSPLANTATION PROCEEDINGS, vol. 28, no. 6, December 1996 (1996-12), pages 3106-3109, XP002215678 See whole document -----	1-5

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/15859

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-5
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-5 are directed to a method of treatment of the human or animal body , the search has been carried out and based on the alleged effects of the compounds/compositions.

2. [X] Claims Nos.: 1
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 1.2

Claims Nos.: 1

Present claim 1 relates to compounds defined by reference to a desirable characteristic or property, namely " NFKAPPA-B inhibitors ".

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and / or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds, In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Independent of the above reasoning, the claims also lack clarity (Article 6 PCT) . An attempt is made to define the compounds by refernce to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds defined in claim 3:
2-chloro-N-[3,5-di(trifluoromethyl)phenyl]-4-(trifluoromethyl)pyrimidine-5-carboxamide; 3,4-dihydro-4,4-dimethyl-2H-1,2-benzoselenazine; declopramide; and dexlipotam in addition to known defined NF-kappa-B inhibitors.

The applicants attention is drawn to the fact that some compounds may be already known to treat the diseases/disorders claimed by the applicant but are as yet not identified as NF-kappa-B inhibitors.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

nformation on patent family members

Intel ınal Application No
PCT/US 02/15859

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5968920 A	19-10-1999	FR 2718441 A	13-10-1995
		AU 692542 B	11-06-1998
		AU 2311195 A	30-10-1995
		CA 2164642 A	19-10-1995
		DE 69521465 D	02-08-2001
		DE 69521465 T	29-05-2002
		DE 701554 T	10-10-1996
		DK 701554 T	08-10-2001
		EP 0701554 A	20-03-1996
		ES 2161879 T	16-12-2001
		WO 9527706 A	19-10-1995
		JP 11501005 T	26-01-1999
		US 6093532 A	25-07-2000